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# RAPID REGENERATION OF THE DERMAL–EPIDERMAL JUNCTION AFTER PARTIAL SEPARATION BY VACUUM: AN ELECTRON MICROSCOPIC STUDY

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A process of rapid repair of dermal–epidermal adherence, as found in experiments with interrupted suction, was investigated electron microscopically. Biopsies in different stages of the process of suction blister formation and of the repair process were studied.

Results show that suction blister formation occurs by successive detachment of hemidesmosomes from the basement membrane, and that, after partial separation of the epidermis from the dermis, a rapid regeneration of the dermal–epidermal junction takes place. This regeneration process apparently consists of two steps: realignment of basal cells to the basement membrane accompanied by autophagocytosis of detached hemidesmosomes, and de novo formation of hemidesmosomes.

The time required for this structural regeneration corresponds well with the speed of the functional repair of dermal–epidermal adherence measured with the technique of interrupted suction.

Local exposure of human skin to a reduced pressure is known to induce subepidermal blistering. Vacuum blisters show a clear-cut separation between epidermal and dermal tissues: under the light microscope the PAS-positive basement zone is seen lining the blister floor [2] and electron microscopy [3] has shown that the level of separation is between the plasma membrane of basal cells and the basement membrane.

Results of previous experiments concerning the influence of suction pressure and local skin temperature on the speed of blister formation [2,4–6] allowed a hypothesis of dermal–epidermal separation in terms of a process of viscous slip, suggesting that some highly viscous resistance was playing a major role in the normal adherence of the epidermis to the dermis [2,6]. The precise location of the viscous slip process with regard to the structural elements of the dermal–epidermal junction remained unknown.

In 1967 Kiistala and Mustakallio reported ultrastructural observations on suction blister formation [3]. After exposure of the skin to vacuum until the first small blisters appeared, they biopsied nonblistered areas adjacent to the blisters in order to study the initial events of blister formation. They concluded that hemidesmosomes are the sites of actual dermal–epidermal adherence because blister formation seemed to start between adjacent hemidesmosomes. However, the questions of how the disconnection of hemidesmosomes occurred, and how this process proceeded with time remained open.

In experiments with interrupted suction the occurrence of a process of rapid repair of dermal–epidermal adherence was found [7]. After initial suction during half of the blistering time, an interval of only about 2 hr sufficed for complete functional repair of dermal–epidermal adherence; by then the connection had regained its full initial strength.

In order to obtain more information on the processes of suction blister formation and repair of dermal–epidermal adherence, an electron microscopic study was undertaken, the results of which will be presented here.

## MATERIALS AND METHODS

Suction experiments were performed on the back of a healthy male volunteer, aged 27 years. The suction apparatus has been described elsewhere [6]. Suction pressure was 250 mm Hg below atmospheric pressure; local skin temperature during the exposure was kept at 36°C. Under these circumstances the exposure time needed for the first visible blister(s), blistering time $t_b$, was about 1 hr. The exposure orifice was 10 mm in diameter. Eight skin specimens were taken by punch biopsy (diameter 3 mm), always centrally in the exposed areas, at various stages of the process of suction blister formation and of the repair process. At the sites of biopsies, blistering times were estimated from results previously obtained on adjacent skin sites (cf [7]).

In the first experimental session 5 biopsies were taken. One was an unexposed control specimen, 4 were taken after suction times of $\frac{1}{4}t_b$, $\frac{1}{2}t_b$, $\frac{3}{4}t_b$, and $t_b$, respectively. In the second session the repair process was studied by

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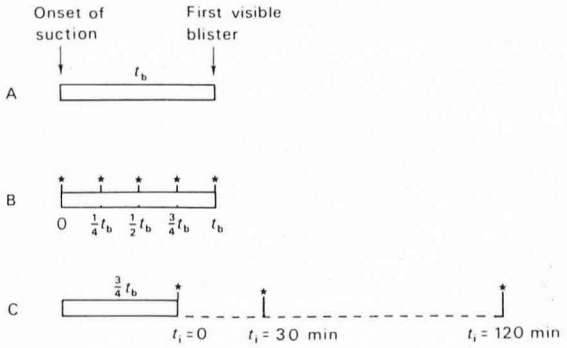



FIG. 1: Outline of experiments. *A:* Blistering time $t_b$ is suction time needed for producing the first blister(s) of 0.5 to 1 mm in diameter. *B:* In the first experimental session 5 biopsies were taken during the course of the separation process. *C:* In the second session 3 biopsies were taken at different intervals, $t_i$, after an initial suction exposure of $\frac{3}{4}t_b$.

taking biopsies at different intervals, $t_i$, after an initial suction period of $\frac{3}{4}t_b$. Three biopsies were taken, at $t_i$ = 0, $t_i$ = 30 min, and $t_i$ = 120 min, respectively (Fig. 1).

Skin biopsies were taken without anesthesia, and immediately immersed in Veronal-buffered 1% $OsO_4$ (pH 7.4). They were cut with a tissue slicer perpendicularly to the skin surface into pieces with a surface area of less than 1 $mm^2$. After fixation in the same solution at 0 to 4°C for 2 hr the material was stained with 1% uranyl acetate for 30 min, dehydrated in ethanol, and embedded in Epon 812. Tissue pieces were trimmed so that only the epidermis and the upper dermis remained. Ultrathin transverse sections were cut with an LKB ultramicrotome, poststained with lead citrate, and studied in a Siemens Elmiskop I electron microscope.

## OBSERVATIONS

### *Unexposed Skin*

The morphology of unexposed skin served as a reference. The ultrastructure of normal skin has been described by various authors [8,9], and only some features of special significance to the present study will be noted here. In epidermal keratinocytes, bundles of tonofilaments are localized in a rounded cage-like structure enclosing the nucleus and the central cytoplasm (Fig. 2). Offshoots of this filament system traverse the outer cytoplasm and run to the desmosomes in the interdigitated membranes of apposing cells, thus forming the so-called desmosomal–tonofibrillar complex of the epidermis. At the dermal side of the basal cells, tonofibrils end at the junctional desmosomes, hemidesmosomes. Hemidesmosomes are connected to the basement membrane by the so-called anchoring filaments [10,11], which can be seen crossing the lamina lucida (Fig. 3). At the dermal side of the basement membrane there is a zone of anchoring fibrils (Fig. 3) which is believed to anchor the basement membrane to the dermal collagen [12,13].

### *The Separation Process*

Three main changes were observed in skin which had been subjected to suction: intracellular vacuoles, extracellular edema, and dermal–epidermal separation. These aspects will be described separately.

*Paranuclear vacuoles.* The regular occurrence of intracellular vacuoles as a result of suction was first noted by Copeman [14] under the light microscope. In most of the epidermal keratinocytes of exposed skin we could find vacuoles in juxtanuclear position. At $t = \frac{1}{4}t_b$ some of these vacuoles were relatively small (Figs. 4, 5). Sometimes, there was still normal cytoplasm containing various organelles between the small vacuoles and the nucleus, and on occasion the vacuoles seemed to be continuous with cisternae of the endoplasmic reticulum. The larger vacuoles usually had a round or oval shape (Fig. 6). Often their surface membranes exhibited irregular foldings, mostly at the side distally to the nucleus. The vacuoles had a distorting influence on the cells' nuclei from which they were separated only by a thin rim of cytoplasm (50–100 nm) (Fig. 6).

At $t = \frac{1}{2}t_b$ vacuoles measured up to 10 $\mu$m in diameter. There was no noticeable growth of the vacuoles after $t = \frac{1}{2}t_b$. Vacuoles mostly contained an amorphous material of low electron density, but sometimes the central part, or even the whole vacuole, remained free of this. In the later stages of blister formation, melanosomes devoid of lining membranes were occasionally seen inside the vacuoles, but this observation was much more common during regeneration of the dermal–epidermal junction (see below). In exposed skin, tonofibrils in epidermal keratinocytes appeared to us more stretched than normally (Fig. 7).

*Intercellular edema.* Between adjacent desmosomes, widening of intercellular spaces occurred. The desmosomal junctions did not seem to be affected by the suction forces, but very often desmosomes were seen apart from one, or both, of the apposing cells (Fig. 7). Most of these observations may be due to oblique sectioning of long cytoplasmic bridges between the cells. Occasionally, however, extracellular cytoplasmic material was found in such places, suggesting rupture of cell membranes. The intercellular edema was most conspicuous at the lateral sides of the basal cells, where redundant plasma membrane is normally present in numerous microvilli, and where comparatively few desmosomes are present per unit area of cell membrane [15]. Widening of intercellular spaces was seen in all the observed stages of suction blister formation, but tended to increase with the duration of the exposure.

*Dermal–epidermal separation.* Actual separation of the epidermis from the dermis occurred by detachment of hemidesmosomes from the basement membrane. Detached hemidesmosomes showed on the dermal face of the plasma membrane, many minute filaments of about equal lengths (±70 nm) forming a brush border on the surface. Detached hemidesmosomes may be seen in Figures 5, 8, 9, and 10. Where hemidesmosomes were detached, no marks of the previous attach-



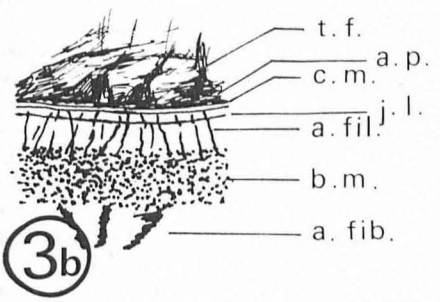



FIG. 2: Electron micrograph of lower part of normal epidermis. Nucleus (*n*) of keratinocyte can be seen surrounded by spherically orientated tonofibrils (*single arrows*). Tonofibrillar cages around nuclei are interconnected by other bundles of tonofibrils (*double arrows*) running via desmosomes. One cage appears to be sectioned obliquely (*arrowhead*). (*d*), Desmosomes; (*hd*), hemidesmosomes; (*D*), dermis; (*E*), epidermis (× 4,500).

FIG. 3. *a*: Hemidesmosome in normal skin (×106,000). *b*: Schematization of 3*a*. (*t.f.*). Tonofibrils; (*a.p.*), attachment plaque; (*c.m.*), cell membrane; (*j.l.*), juxtamembranous layer; (*a.fil.*), anchoring filaments crossing the lamina lucida; (*b.m.*), basement membrane; (*a.fib.*), anchoring fibrils.

ment could be observed at the overlying basement membrane, which indicated that the anchoring filaments were lifted with the hemidesmosomes. The basement membrane itself and the region of the anchoring fibrils underneath remained unchanged throughout suction blister formation. However, by way of exception, rupture of the basement membrane has been observed.

Separation of epidermis from dermis appeared to be a gradual process. At time $t = \frac{1}{4}t_b$ only a few hemidesmosomes were detached (Fig. 4). Larger parts of basal cell membranes could be found separated at time $t = \frac{1}{2}t_b$, while at $t = \frac{3}{4}t_b$ some basal cells were even completely separated from the basement membrane. Detachment of individual basal cells seemed to start laterally, the central part of a cell remained adherent to the last (Fig. 7). In places of separation the space between epidermis and dermis was occasionally bridged by very slender threads of cytoplasm. At $t = t_b$ (when macroscopic blistering becomes visible), microscopic separation was seen over large distances. In places of separation, small membrane-lined parts of keratinocytes could be observed at the basement membrane, even if separated parts seemed to be displaced over appreciable distances. This observation suggested rupture of cell membranes in the final stages of the separation process.

The above observations of dermal–epidermal separation should be considered as indicating only the most advanced state of the separation process at the time of observation. That is, in a biopsy at a certain exposure time, the whole range of morphologic features of all previous biopsies may be found, so that even a normal-looking dermal–epidermal junction as well as places with only minor separation can be found at $t = t_b$.

### *The Regeneration Process*

In previous experiments on repair of dermal–epidermal adherence [7], suction was interrupted after an initial exposure of the skin during half of the blistering time ($t = \frac{1}{2}t_b$). In the present study, however, repair was investigated after suction during three-quarters of the blistering time ($t = \frac{3}{4}t_b$). The more progressive separation at $t = \frac{3}{4}t_b$ was expected to give a better opportunity for microscopic observation of the repair process. Besides, we knew from unpublished observations that functional repair of dermal–epidermal adherence follows approximately the same function of time,

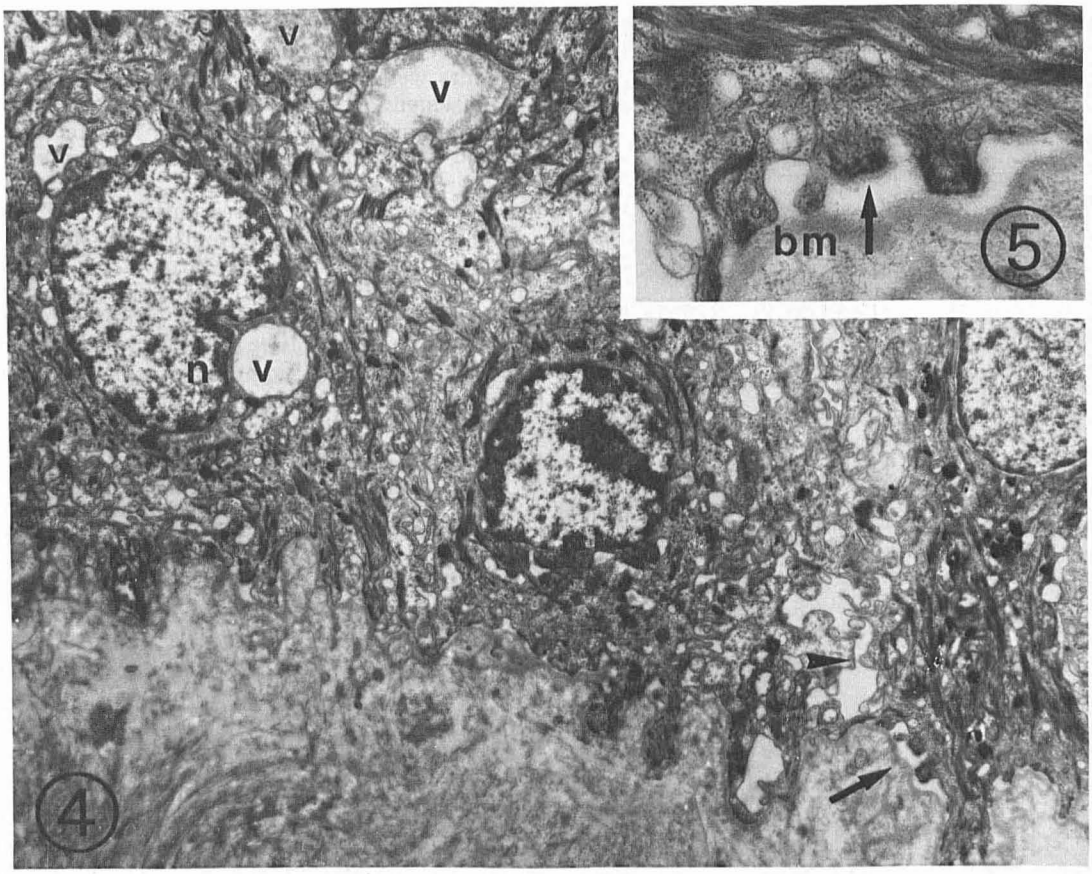



FIG. 4: Earliest stage of suction blister formation observed, $\frac{1}{4}t_b$. Small juxtanuclear vacuoles (*v*) are present in most of the cells. The vacuoles seem to distort cell nuclei (*n*). There is some widening of the space between adjacent basal cells (*arrowhead*), and minimal dermal–epidermal separation at the basement membrane (*arrow*; cf Fig. 5) (× 4,500).

FIG. 5: Partial separation at dermal–epidermal junction at $\frac{1}{4}t_b$. Magnified part of Figure 4 showing that dermal–epidermal separation is through the lamina lucida and occurs by detachment of hemidesmosomes from the basement membrane. Detached hemidesmosome (*arrow*) is bordered with remnants of anchoring filaments. Basement membrane (*bm*) looks unaffected (× 18,000).

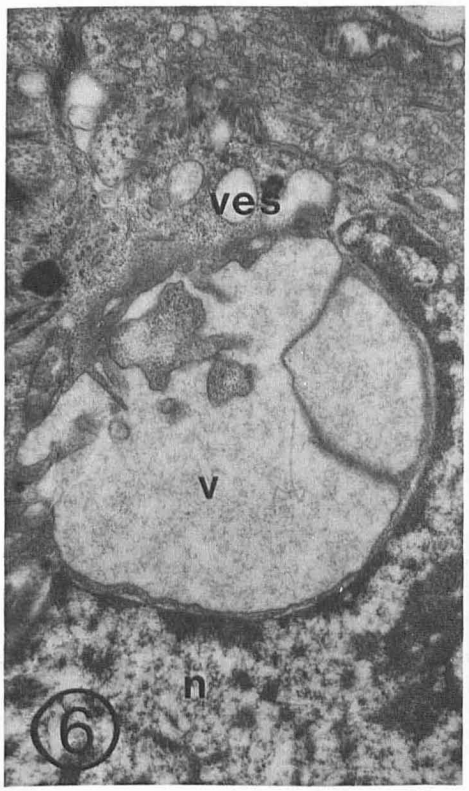
whether measured after an initial exposure of $\frac{3}{4}t_b$ or $\frac{1}{2}t_b$; this suggests that basically the same processes are involved.

The biopsy taken at $t_i = 0$ (cf Fig. 1) served as a reference for the observations on repair. As expected from the observations in the first part of this study this biopsy showed large paranuclear vacuoles, intercellular edema, and an advanced stage of dermal–epidermal separation (Fig. 7). These three aspects were studied at two different repair intervals, $t_i = 30$ min and $t_i = 120$ min.

*Paranuclear vacuoles.* Although some changes occurred in the appearance of the paranuclear vacuoles within epidermal keratinocytes, the vacuoles did not vanish within 2 hr after suction. At $t_i = 30$ min the vacuoles had become a little smaller and had a less rounded shape than at $t_i = 0$. They were completely filled with an amorphous material containing distinct particles most of which were like melanosomes without a lining membrane. At $t_i = 120$ min the vacuoles were still present and contained even more melanosome-like particles (Fig. 11).

*Intercellular edema.* At $t_i = 30$ min, intercellular spaces looked much less enlarged than at $t_i = 0$. The tonofibrillar system appeared unstretched. Desmosomes were intact themselves but intercellular contacts were not as regular as in normal skin. In the plane of section many desmosomes appeared to be connected to only one cell, suggesting excessive folding of cell membranes. This was probably due to the stretching of intercellular bridges during the exposure to suction. Intercellular remnants of desmosomes were not observed. At $t_i = 120$ min, intercellular contacts and the desmosomal–tonofibrillar system did not noticeably differ from normal (Fig. 11).

*Regeneration of the dermal–epidermal junction.* Some remarkable phenomena occurred at the dermal–epidermal junction during the repair interval. At $t_i = 30$ min pseudopod-like protrusions of basal cells could be found in contact with the basement membrane in places where dermal–epidermal separation had occurred (Fig. 8). The actual contact between the membrane of the protrusions and the basement membrane was mostly made by fine



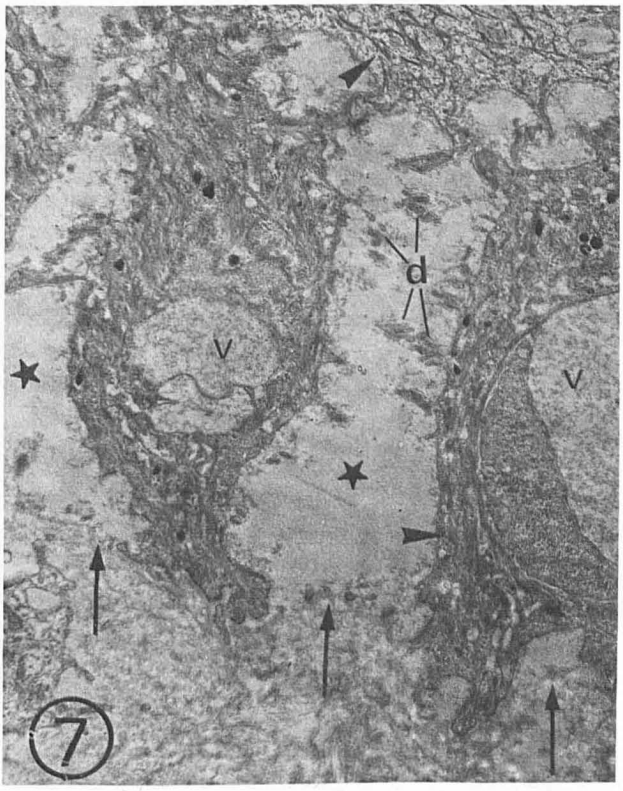




FIG. 6: Juxtanuclear vacuole ($v$) at $\frac{1}{4}t_b$. A thin rim of cytoplasm is present between the vacuole and the distorted cell nucleus ($n$). Note the irregularity of the vacuolar membrane and the small vesicles (*ves*) suggesting growth of the vacuole by fusion with smaller vacuoles (× 12,000).

FIG. 7: Basal cell after suction during $\frac{3}{4}t_b$ (or $t_i$ = 0, the beginning of the repair interval). Large intracellular vacuoles ($v$), extreme widening of intercellular spaces (*asterisks*) especially between basal cells, progressive separation at dermal–epidermal junction (*arrows*). Only the middle portion of the basal cell shown is attached to the dermis Note apparently isolated desmosomal structures ($d$) and stretched tonofibrils (*arrowheads*) (× 6,000).

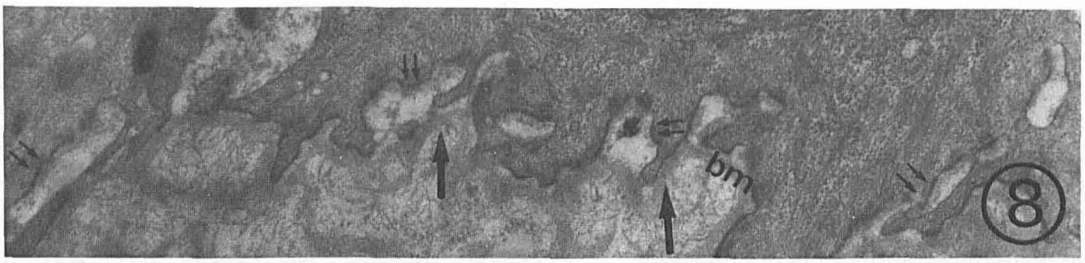
filaments resembling the anchoring filaments of hemidesmosomes. Disconnected hemidesmosomes were frequently observed on the lateral sides of basal cells.

In other places observed at $t_i$ = 30 min there was a complete lining-up of keratinocytes with the basement membrane, while autophagic vacuoles lay at about 0.2 μm from the basement membrane. These vacuoles still contained detached hemidesmosomes on their edges (Figs. 9, 10). In such regions, structures looking like incomplete hemidesmosomes could be seen, consisting of a thickened cell membrane and a local concentration of fine filaments running between cell membrane and basement membrane (Fig. 9). In regions where autophagic vacuoles testified to previous detachment, the majority of hemidesmosome-like structures observed at 30 min of repair ($t_i$ = 30 min) lacked the juxtamembranous layer.

At $t_i$ = 120 min the hemidesmosomes generally looked regular and complete, and the dermal–epidermal junction showed a normal aspect (Figs. 11, 12). However, electron-dense bodies consisting of a thick, dense membrane with an amorphous content could be found near the basement membrane (Fig. 12). Most probably these bodies are remnants of the phagocytic vacuoles observed at $t_i$ = 30 min, which bore on their membranes the detached hemidesmosomes.

## DISCUSSION

*Edema of the epidermis.* The juxtanuclear vacuoles which develop in epidermal keratinocytes on exposure to suction have recently been studied ultrastructurally by Hunter, McVittie, and Comaish [16]. Most of our findings on these vacuoles agree with their observations. Similar vacuoles have earlier been reported in dermographic edema [17] and after intradermal injection of hypertonic fluids [18]. The latter observation was reported by Hönigsmann and Wolff who found that the endoplasmic reticulum of the keratinocytes communicated directly with the intercellular space, and they ascribed the vacuoles to an unfolding of the reticulum by means of direct osmotic action over its membrane. These authors suggested the communications between reticulum and intercellular space to be open only under special circumstances, e.g., when in contact with hypertonic solutions. Hunter et al [16] inferred that adequate circumstances to open the communications might also exist during a period of suction.



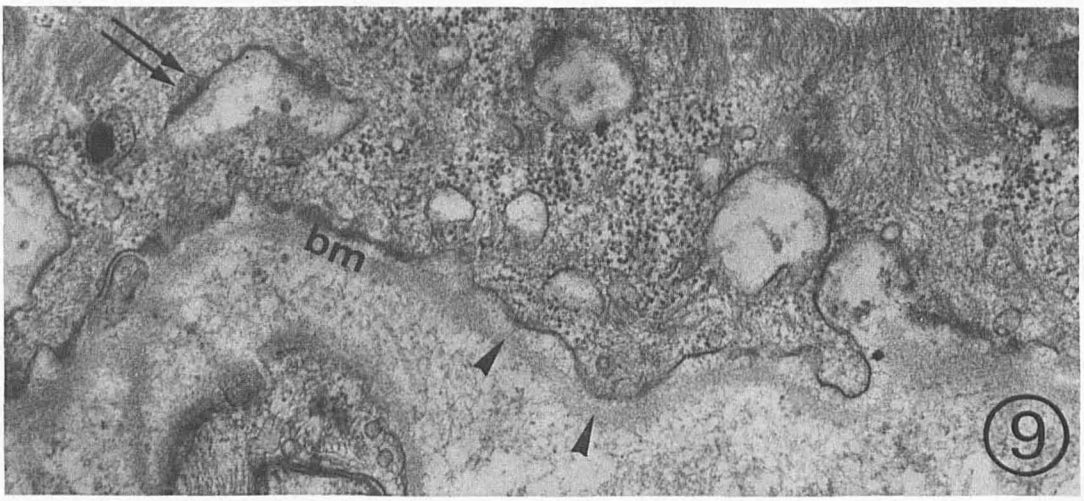




FIG. 8: Early events in regeneration of dermal–epidermal junction as observed half an hour ($t_1$ = 30 min) after initial suction during $\frac{3}{4}t_b$. Epidermal cell protrusions (*arrows*) are seen in contact with the basement membrane (*bm*), leaving behind the detached hemidesmosomes (*double arrows*) (× 15,000).

FIG. 9: Dermal–epidermal junction at $t_1$ = 30 min. Regeneration is apparently in a further stage here than observed in Figure 8. Remnants of detached hemidesmosomes appear to be interior to the cell (*double arrow*). The basement membrane (*bm*) is lined with cell membrane. Local concentrations of anchoring filaments may be seen (*arrowheads*) in absence of true hemidesmosomes (× 25,000).

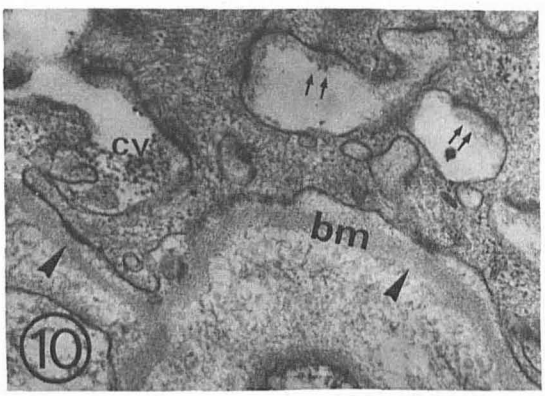



FIG. 10: Regenerative processes at dermal–epidermal junction at $t_1$ = 30 min. Detached hemidesmosomes bordered with anchoring filaments may be seen at the edges of intracellular vacuoles (*double arrows*). Electron-dense places along the dermal–epidermal junction (*arrowheads*) seem to indicate formation of new hemidesmosomes. Note some extracellular cytoplasm in this micrograph (*cy*) (× 22,000).

It seems obvious that after some time of suction the hydrostatic pressure gradient in the skin resulting from the suction pressure will be almost entirely over the epidermal horny layer since this layer contains the skin's water barrier. For a hydrostatic pressure difference to build up over the horny layer, a sufficient amount of fluid will have to accumulate under that layer, until the tonofibrils are stretched. Fluid will, therefore, accumulate in the epidermis in some way or another. It seems that the typical vacuoles near the cells' nuclei, and the spaces between epidermal cells, are just sites of preference for the fluid to accumulate.

The suggestion that an adequate hydrostatic pressure difference is the decisive factor in the formation of paranuclear vacuoles agrees with the occurrence of similar vacuoles after hypertonic fluid injection [18] or dermographic wheal formation [17]. The rise in hydrostatic fluid pressure inside the skin in these cases will have a similar influence on hydrostatic pressure differences as has a reduction of the hydrostatic pressure outside the skin through vacuum.

Juxtanuclear vacuoles have been found to appear within 3 min of suction on the skin [16]. They do not seem to disappear, however, within 2 hr of repair from suction damage. In that time their sizes decrease, and a simultaneous increase of their electron density indicates concentration of their contents. During the repair interval an increased number of melanosomes has been observed inside the vacuoles. Normally, melanosomes are mem-

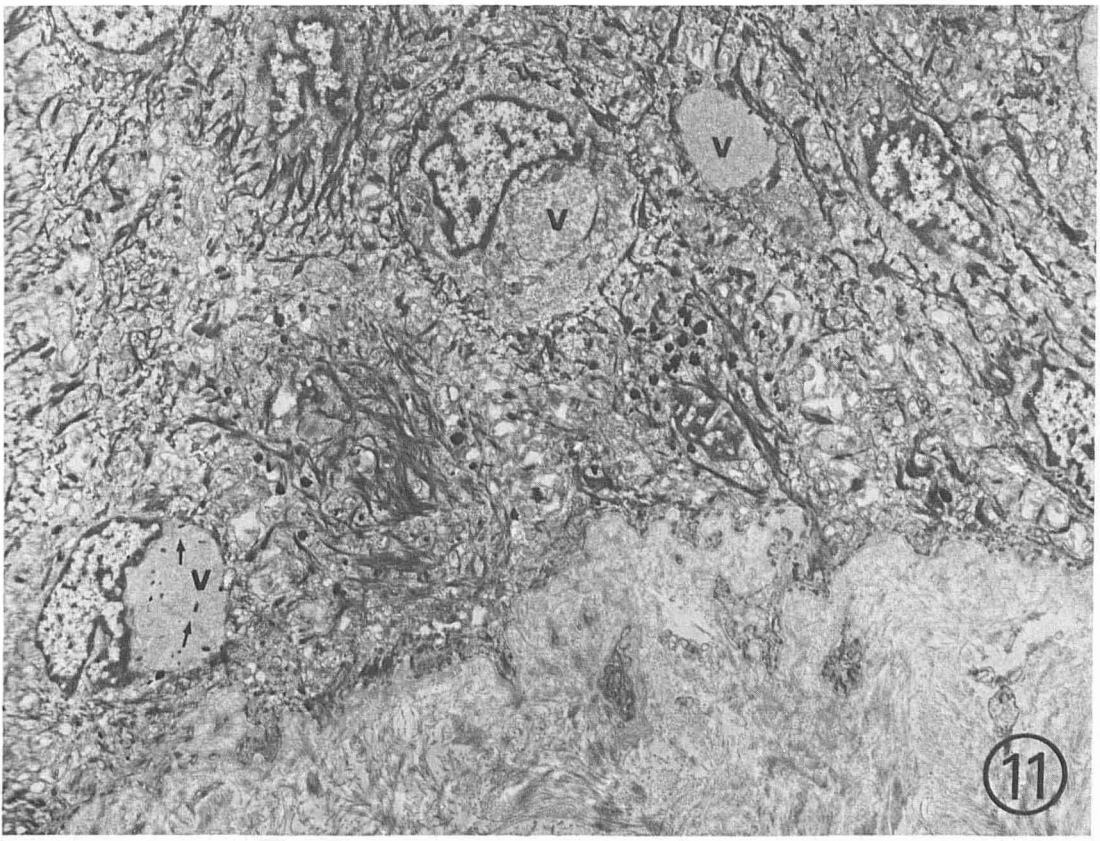




FIG. 11: Lower part of the epidermis at 2 hr ($t_1$ = 120 min) after suction during $^3/_4 t_b$. Paranuclear vacuoles ($v$) are still present. One vacuole contains many melanosomes (*small arrows*). The tonofibrillar system and the intercellular connections appear normal. Dermal–epidermal junction shows no separation (× 6,000).

FIG. 12: Dermal–epidermal junction at 2 hr ($t_1$ = 120 min) after initial suction during $^3/_4 t_b$. Peculiar bodies (*arrows*) near the basement membrane most likely are autophagocytotic vacuoles formed earlier by internalization of detached hemidesmosomes. The dermal–epidermal junction appears normal, so that its regeneration seems completed (× 15,000).

brane-lined [19]. Therefore, our observation that these melanosomes were without lining membranes suggests that the melanosomes entered the vacuoles by fusion of lining membranes. This is in contrast with the suggestion by others [16] that melanosomes entered through damaged sites on the vacuoles.

We feel that the observations on juxtanuclear

vacuoles in epidermal keratinocytes indicate that these vacuoles do not play a significant part in the process of dermal–epidermal separation by vacuum. From the viewpoint of the mechanics of the separation process, the fluid could just as well have accumulated in any other place in the viable epidermis.

*Dermal–epidermal separation.* The present study confirms the findings of Kiistala and Mustakallio [3] with respect to the initial events of blister formation. In addition, it has become clear that separation of the epidermis by vacuum is a gradual process in the sense that the individual hemidesmosome detachment starts soon after the beginning of suction, and that further separation occurs continuously throughout the exposure by the successive detachment of more hemidesmosomes.

Detachment of hemidesmosomes does not seem to affect the morphology of the basement membrane. Hemidesmosomes detached by vacuum show a band of anchoring filaments of about 70 nm length. In normal skin the width of lamina lucida in a hemidesmosome is about 30 nm [8], while the basement membrane is about 40 nm in thickness [8]. This would imply that normally anchoring fibrils may extend through the basement membrane, even down to its dermal side.

The same ultrastructural level of separation between hemidesmosomes and basement membrane as we have found in suction blisters has also been reported for lesions of epidermolysis bullosa hereditaria letalis [20] and in the case of mild freezing blisters [21]. Furthermore, in a study on the effect of chelating agents (EDTA) on the epithelial–connective tissue union in human oral mucosa, an apparently identical plane of separation has been found [22].

Our observations on the detachment of individual hemidesmosomes suggest that it is the connection between anchoring filaments and basement membrane which is loosened when skin is under suction. Therefore, the viscous bond between epidermis and dermis previously proposed as a result of suction experiments [2,6] should be located there. Recently, the possibility has been suggested [22] that linkage of anchoring filaments to the basement membrane material occurs through cationic cross-bridges between polyanionic proteins and/or protein–polysaccharides. Further study will be needed to reveal whether the concept of the dermal–epidermal adherence as a viscous connection is in keeping with the idea of an ionic bond.

*Regeneration of the dermal–epidermal junction.* Our results indicate that a rapid structural regeneration of the dermal–epidermal junction takes place after the junction has been affected by suction. It seems that during this structural regeneration two different biologic processes may be distinguished: realignment of basal cells with the basement membrane, and de novo formation of hemidesmosomes.

In the first instance, partly or almost completely detached basal cells occupy the empty spaces at the basement membrane, especially by means of pseudopod formation. This realignment is accompanied by interiorization of the cells' detached hemidesmosomes (Fig. 13). A process much like this internalization of hemidesmosomes by basal cells has been described by Overton [23,24]. In her studies of reaggregation phenomena between trypsinized epithelial cells, she saw halves of trypsin-split desmosomes become internal to the cells in a way similar to that we have described. Phagocytized halves of desmosomes (semidesmosomes) could be observed within 20 min after trypsinization [23]. Recently a process of interiorization of hemidesmosomes at the inferior side of basal cells has been described to occur after separation of the epithelium and the connective tissue of human oral mucosa which had previously been incubated in an enzyme solution [25]

The facts that hemidesmosomes are phagocytized and that in about 2 hr the dermal–epidermal junction becomes normal, indicate that a second process is involved in the regeneration of the

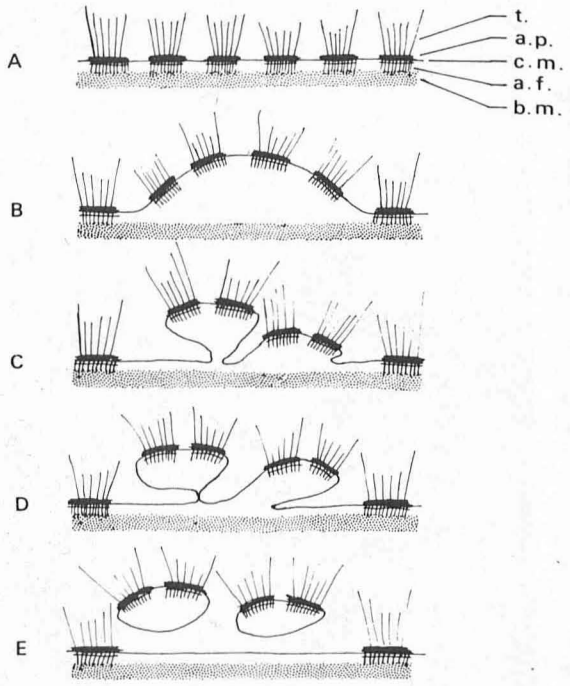



FIG. 13: Schematic representation of partial separation of epidermis and dermis by vacuum, and the subsequent internalization of detached hemidesmosomes by basal cells. During exposure to suction, anchoring filaments (*A*) become detached from the basement membrane (*B*). If skin is left at rest after partial separation, pseudopod-like protrusions of basal cells make contact with and move along the basement membrane (*C*) so that detached hemidesmosomes become invaginated (*D*) and finally internal to the cell (*E*). In this scheme no attention has been paid to the formation of new hemidesmosomes which, however, probably occurs to some extent simultaneously.

junction, namely de novo formation of hemidesmosomes. This conclusion is supported by the observation that many hemidesmosomal structures at 30 min of repair looked incomplete. De novo formation of hemidesmosomes obviously occurs in migrating keratinocytes in epidermal wound healing [26,27]. Krawczyk has described the morphogenesis of hemidesmosomes in wound healing in about 1-mm suction blisters in mouse skin [27]. He differentiated four stages in the formation process: extension of anchoring filaments, formation of the juxtamembranous layer, formation of the attachment plaque, and insertion of the tonofibrils. The author did not investigate the time course of the formation process, but hemidesmosome-like structures apparently in the third phase may be discerned in his micrographs (see Fig. 1 of [27]) at only about 5 $\mu$m behind the advancing tip of the epithelial sheet. Since epidermal migration on moist wound surfaces has been found to occur at a speed of 10 to 20 $\mu$m/hr [28] the data suggest that hemidesmosome formation may take place within 1 hr.

Previous work on suction blistering [7] has demonstrated a process of rapid repair of dermal-epidermal adherence, the nature of which could be either physical (passive) or biologic (active). It has been shown in this study that localized microscopic separation between epidermis and dermis occurs long before macroscopic suction blistering becomes visible, and that structural regeneration of the dermal-epidermal junction after such partial separation is about completed in 2 hr from cessation of suction. This time is of the same magnitude as the intervals needed for complete functional repair of dermal-epidermal adherence in experiments with interrupted suction [7]. This indicates that the observed structural regeneration is likely to be the basis of the functional repair of dermal-epidermal adherence, which would favor the hypothesis that repair of dermal-epidermal adherence is an active process.

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